Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Abacavir (ABC, Ziagen) (Last updated August 11, 2011; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric oral solution: 20 mg/mL

Tablets: 300 mg (scored)

Combination tablets:

- *With lamivudine (3TC):* ABC 600 mg + 3TC 300 mg (Epzicom)
- *With zidovudine (ZDV) and 3TC:* ABC 300 mg + ZDV 300 mg + 3TC 150 mg (Trizivir)

Dosing Recommendations

Neonate/infant dose:

- Not approved for infants aged <3 months.

Pediatric dose:

- *Oral solution (≥3 months of age):*
  8 mg/kg (maximum 300 mg) twice daily.

  In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte count, can consider using once-daily abacavir dosing: 16 mg/kg/dose to maximum of 600 mg once daily (see text).

Scored 300 mg tablet (weight ≥14 kg):

Weight (kg)	Twice-Daily Dosage Regimen		
	AM Dose	PM Dose	Total Daily Dose
14–21 kg	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21–<30 kg	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30 kg	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Adolescent (aged ≥16 years)/adult dose:

- 300 mg twice daily or 600 mg once daily.

Trizivir

- *Adolescent (weight ≥40 kg)/adult dose:*
  One tablet twice daily.

Selected Adverse Events

- Hypersensitivity reaction that may be fatal; symptoms may include fever; rash; nausea; vomiting; malaise or fatigue; loss of appetite; respiratory symptoms such as sore throat, cough, shortness of breath.
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of ABC; however, other studies have not substantiated this finding, and there are no data in children.

Special Instructions

- Test patients for the HLA-B*5701 allele before starting therapy to predict risk of hypersensitivity; patients with the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested.
- ABC can be given without regard to food.
- Caution patients and parents about risk of serious HSR that can be fatal. Do not re-challenge.

Metabolism

- Metabolized by alcohol dehydrogenase and glucuronyl transferase; renal excretion of metabolites 82%.
- ABC requires dosage adjustment in hepatic insufficiency. Do not use Trizivir and Epzicom (fixed-dose combination products) in patients with creatinine clearance (CrCl) <50 mL/min,

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Epzicom

- *Adolescent (≥16 years of age)/adult dose:* One tablet once daily.

patients on dialysis, or those with impaired hepatic function.

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Didanosine (ddI, Videx) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Videx pediatric powder for oral solution: reconstituted 10 mg/mL

Videx enteric-coated (EC) delayed-release capsules (EC beadlets): 125 mg, 200 mg, 250 mg, and 400 mg

Generic ddI delayed-release capsules: 200 mg, 250 mg, and 400 mg

Dosing Recommendations

Neonate/infant dose (aged 2 weeks to <3 months):

- 50 mg/m^2 of body surface area every 12 hours.
- Manufacturer recommends 100 mg/m^2 of body surface area every 12 hours in this age range. Panel members interpret pharmacokinetic data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m^2 of body surface area every 12 hours.

Infant dose (aged ≥3 months to 8 months):

- 100 mg/m^2 of body surface area every 12 hours.

Pediatric dose of oral solution (age >8 months):

- 120 mg/m^2 of body surface area every 12 hours.

  (Dose range: 90–150 mg/m^2 of body surface area every 12 hours; maximum dose 200 mg/dose twice daily.)

Pediatric dose of Videx EC or generic capsules (aged 6–18 years and body weight ≥20 kg):

Body Weight (kg)	Dose (mg)
20 kg to <25 kg	200 mg once daily
25 kg to <60 kg	250 mg once daily
≥60 kg	400 mg once daily

In treatment-naive children aged 3–21 years, 240 mg/m^2 of body surface area once daily (oral solution or capsules) has been used with effective viral suppression.

Selected Adverse Events

- Peripheral neuropathy
- Electrolyte abnormalities
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in adults. (The risk is increased when ddI is used in combination with stavudine [d4T].)
- Pancreatitis (less common in children than in adults, more common in adults when ddI is used in combination with tenofovir [TDF] or d4T)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Because food decreases absorption of ddI, administration of ddI on an empty stomach (30 minutes before or 2 hours after a meal) generally is recommended. To improve adherence, some practitioners administer ddI without regard to timing of meals (see text below).
- ddI oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual protease inhibitor for instructions on timing of administration. This interaction is more pronounced for the buffered (solution) formulation of ddI, than for the enteric coated formulation.

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Adolescent/adult dose:

Body Weight (kg)	Dose (mg)
<60 kg	250 mg once daily
≥60 kg	400 mg once daily

ddI in combination with TDF:

- This combination should be avoided, if possible, because of enhanced ddI toxicity.

Pediatric/adolescent dose of ddI when combined with TDF:

- No data on this combination in children or adolescents aged <18 years, but decrease in ddI dose is recommended as in adults.

Adult dose of ddI when combined with TDF:

Body Weight (kg)	Dose (mg)
<60 kg (limited data in adults)	200 mg once daily
≥60 kg	250 mg once daily

- Shake ddI oral solution well before use. Keep refrigerated; solution is stable for 30 days.

Metabolism

- Renal excretion 50%.
- Dosing of ddI in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

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Emtricitabine (FTC, Emtriva) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric oral solution: 10 mg/mL

Capsules: 200 mg

Combination tablets

- *With tenofovir (TDF):* 200 mg FTC + 300 mg TDF (Truvada)
- *With TDF and efavirenz (EFV):* 200 mg FTC + 300 mg TDF + 600 mg EFV (Atripla)
- *With TDF and rilpivirine (RPV):* 200 mg FTC + 300 mg TDF + 25 mg RPV (Complera)
- *With FTC + elvitegravir (EVG) + cobicistat (COBI):* 200 mg FTC + 150 mg EVG + 150 mg COBI + 300 mg TDF (Stribild)

Dosing Recommendations

Neonate/infant dose (aged 0–<3 months):

- *Oral solution:* 3 mg/kg once daily.

Pediatric dose (aged ≥3 months–17 years):

- *Oral solution:* 6 mg/kg (maximum dose 240 mg) once daily. (Higher maximum dose because the oral solution has 20% lower plasma exposure in pediatric pharmacokinetic analysis.)
- *Capsules (for children who weigh >33 kg):* 200 mg once daily.

Adolescent (aged ≥18 years)/adult dose:

- *Oral solution:* 240 mg (24 mL) once daily.
- *Capsules:* 200 mg once daily.

Combination Tablets

Truvada

- *Adolescent (aged ≥12 years and ≥35 kg) and adult dose:* 1 tablet once daily.

Atripla

- *Adolescent (aged ≥12 years and ≥40 kg) and adult dose:* 1 tablet once daily.
- See efavirenz section for pregnancy warning.

Complera

- *Adult dose (aged ≥18 years):* 1 tablet once daily.

Selected Adverse Events

- Minimal toxicity.
- Severe acute exacerbation of hepatitis can occur in hepatitis B virus (HBV)-coinfected patients who discontinue FTC.
- Hyperpigmentation/skin discoloration on palms and/or soles.

Special Instructions

- FTC can be given without regard to food; however, administer Atripla on an empty stomach because it also contains EFV.
- FTC oral solution can be kept at room temperature up to 77°F (25°C) if used within 3 months; refrigerate for longer term storage.
- Before using FTC, screen patients for HBV.

Metabolism

- Limited metabolism: No cytochrome P (CYP) 450 interactions.
- Renal excretion 86%: Competition with other compounds that undergo renal elimination.
- Dosing of FTC in patients with renal impairment: Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use Atripla (fixed-dose combination) in patients with creatinine clearance (CrCl) <50

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Stribild: • *Adult dose (aged ≥18 years):* 1 tablet once daily in treatment-naive adults. Administer with food.	mL/min or in patients requiring dialysis. • Do not use Truvada (fixed-dose combination) in patients with CrCl <30 mL/min or in patients requiring dialysis. • Use Complera with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease. • If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

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Lamivudine (3TC/Epivir) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral solution: 10 mg/mL (Epivir), 5 mg/mL (Epivir HBVa)

Tablets: 150 mg (scored) and 300 mg (generic and Epivir); 100 mg (Epivir HBV[a])

Combination tablets:

- *With zidovudine (ZDV):* 150 mg 3TC + 300 mg ZDV (generic and Combivir)
- *With abacavir (ABC):* 300 mg 3TC + 600 mg ABC (Epzicom)
- *With ZDV and ABC:* 150 mg 3TC + 300 mg ZDV + 300 mg ABC (Trizivir)

[a] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The strength of 3TC in Epivir HBV solution and tablet was maximized for treatment of hepatitis B virus (HBV) only. If Epivir HBV is used in HIV-infected patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen. The Epivir HBV tablet is appropriate for use in children who require a 100 mg 3TC dose for treatment of HIV infection.

Dosing Recommendations

Neonate/infant dose (age <4 weeks) for prevention of transmission or treatment:

- 2 mg/kg twice daily.

Pediatric dose (age ≥4 weeks):

- 4 mg/kg (up to 150 mg) twice daily.

Pediatric dosing for scored 150-mg tablet (weight ≥14 kg):

Weight (kg)	AM dose	PM dose	Total Daily Dose
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21–<30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Adolescent (age ≥16 years)/adult dose:

- *Body weight ≥50 kg:*
  150 mg twice daily or 300 mg once daily.
- *Body weight <50 kg:*
  4 mg/kg (up to 150 mg) twice daily.

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of 3TC in the setting of chronic hepatitis B infection.

Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before administering 3TC.

Metabolism

- Renal excretion—dosage adjustment required in renal insufficiency.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function

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Combivir

- *Adolescent (weight ≥30 kg)/adult dose:*
  1 tablet twice daily.

Trizivir

- *Adolescent (weight >40 kg)/adult dose:*
  1 tablet twice daily.

Epzicom

- *Adolescent (age >16 years and weight >50 kg)/adult dose:*
  1 tablet once daily.

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Stavudine (d4T, Zerit) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, 40 mg

Generic: d4T capsules and solution have been approved by the Food and Drug Administration (FDA) for manufacture and distribution in the United States.

Dosing Recommendations

Neonate/infant dose (birth to 13 days):

- 0.5 mg/kg twice daily.

Pediatric dose (at least 14 days old and weighing <30 kg):

- 1 mg/kg twice daily

Adolescent (≥30 kg)/adult dose:

- 30 mg twice daily.

Selected Adverse Events

- Mitochondrial toxicity
- Peripheral neuropathy
- Lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other nucleoside reverse transcriptase inhibitors [NRTIs]). The risk is increased when used in combination with ddI.
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- d4T can be given without regard to food.
- Shake d4T oral solution well before use. Keep refrigerated; the solution will remain stable for 30 days.

Metabolism

- Renal excretion 50%. Decrease dose in renal dysfunction.

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Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral powder: 40 mg per 1 g of oral powder (1 level scoop = 1 g oral powder; supplied with dosing scoop)

Tablet: 150 mg, 200 mg, 250 mg, and 300 mg

Combination tablets:

- *With emtricitabine (FTC):* 200 mg FTC + 300 mg TDF (Truvada)
- *With FTC + efavirenz (EFV):* 200 mg FTC + 600 mg EFV + 300 mg TDF (Atripla)
- *With FTC + rilpivirine (RPV):* 200 mg FTC + 25 mg RPV + 300 mg TDF (Complera)
- *With FTC + elvitegravir (EVG) + cobicistat (COBI):* 200 mg FTC + 150 mg EVG + 150 mg COBI + 300 mg TDF (Stribild)

Dosing Recommendations

Neonate/infant dose:
Not FDA approved or recommended for use in neonates/infants aged <2 years.

Pediatric dose (aged ≥2 years to <12 years)*:

- 8 mg/kg/dose once daily.

Oral powder dosing table

Body Weight Kilogram (kg)	Oral Powder Once Daily Scoops of Powder
10–<12	2
12–<14	2.5
14–<17	3
17–<19	3.5
19–<22	4
22–<24	4.5
24–<27	5
27–<29	5.5
29–<32	6
32–<34	6.5
34–<35	7
≥35	7.5

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density (BMD)

Special Instructions

- Oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix oral powder in 2–4 oz of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the oral powder with liquid: the powder may float on the top even after vigorous stirring.
- TDF can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. Because Atripla also contains EFV, the combination tablet should be administered on an empty stomach.
- Given the potential for TDF-induced changes in renal tubular function, some panel members recommend monitoring for proteinuria and glycosuria every 6–12 months.

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Tablets dosing table (aged ≥2 years and weight ≥17 kg)

Body Weight Kilogram (kg)	Tablets Once Daily
17–<22	150 mg
22–<28	200 mg
28–<35	250 mg
≥35	300 mg

Adolescent (aged ≥12 years and weight ≥35 kg)* and adult dose:

- 300 mg once daily

  * See text for concerns about decreased bone mineral density (BMD), especially in prepubertal patients and those in early puberty (Tanner Stages 1 and 2).

Combination Tablets

Truvada

- *Adolescent (aged ≥12 years and weight ≥35 kg) and adult dose:* 1 tablet once daily.

Atripla

- *Adolescent (aged ≥12 years and weight ≥40kg) and adult dose:* 1 tablet once daily.

Complera

- *Adult dose:* 1 tablet once daily in treatment-naive adults. Administer with a meal.

Stribild

- *Adult dose (aged ≥18 years):* 1 tablet once daily in treatment-naive adults. Administer with food

TDF in combination with didanosine (ddI):

- The combination of TDF and ddI should be avoided if possible. If used, ddI dose requires modification. See section on ddI.

TDF in combination with atazanavir (ATV):

- When ATV is used in combination with TDF, ATV should always be boosted with ritonavir (RTV).
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Metabolism

- Renal excretion.
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance (CrCl).
- Atripla and Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring dialysis.
- Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

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Zidovudine (ZDV, AZT, Retrovir) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg

Tablets: 300 mg

Syrup: 10 mg/mL

Concentrate for injection or intravenous (IV) infusion: 10 mg/mL

Generic: ZDV capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

Combination tablets:

- *With lamivudine (3TC):* 300 mg ZDV + 150 mg 3TC (Combivir, generic)
- *With 3TC + abacavir (ABC):* 300 mg ZDV + 150 mg 3TC + 300 mg ABC (Trizivir)

Dosing Recommendations

ZDV dose for neonates/infants (<6 weeks of age) for prevention of transmission or treatment (Note: standard neonate dose may be excessive in premature infants)**:**

Gestational Age (weeks)	ZDV Oral Dosing	ZDV Intravenous Dosing (if unable to tolerate oral agents)
≥35 weeks	4 mg/kg of body weight every 12 hours	3 mg/kg of body weight IV every 12 hours
≥30–<35 weeks	2 mg/kg of body weight every 12 hours during first 14 days of life; increased to 3 mg/kg every 12 hours aged ≥15 days	1.5 mg/kg of body weight IV every 12 hours during first 14 days of life; increased to 2.3 mg/kg every 12 hours aged ≥15 days
<30 weeks	2 mg/kg of body weight every 12 hours during first 4 weeks of life; increased to 3 mg/kg every 12 hours after age 4 weeks	1.5 mg/kg of body weight IV every 12 hours until 4 weeks of life; increased to 2.3 mg/kg every 12 hours after age 4 weeks

Selected Adverse Events

- Bone marrow suppression: macrocytic anemia or neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Nail pigmentation
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Lipoatrophy
- Myopathy.

Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develop in patients receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells and platelets.

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Pediatric dose (6 weeks to <18 years of age):

- *Body surface area dosing:*
  Oral: 180–240 mg/m^2 of body surface area every 12 hours or 160 mg/m^2 every 8 hours.

Weight-based dosing:

Body Weight	Twice-Daily Dosing*
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

*Three times daily dosing is approved but rarely used in clinical practice.

Adolescent (age ≥18 years)/adult dose:

- 300 mg twice daily.

Combivir

Adolescent (weight ≥30 kg)/adult dose:

- 1 tablet twice daily.

Trizivir

Adolescent (weight ≥40 kg)/adult dose:

- 1 tablet twice daily.

Metabolism

- Metabolized to AZT glucuronide, which is renally excreted.
- Dosing in patients with renal impairment: Dosage adjustment is required in renal insufficiency.
- Dosing in patients with hepatic impairment: Decreased dosing may be required in patients with hepatic impairment.
- Do not use Combivir and Trizivir (fixed-dose combination products) in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

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Efavirenz (EFV, Sustiva) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 50 mg, 200 mg

Tablets: 600 mg

Combination Tablets:

- *With emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF):*
  FTC 200 mg + TDF 300 mg + EFV 600 mg (Atripla)

Dosing Recommendations

Neonate/infant dose:

- EFV is not approved for use in neonates/infants.

Pediatric dose:

- *Children aged <3 years:*
  No data are currently available on the appropriate EFV dosage for children aged <3 years.
- *Children aged ≥3 years and body weight ≥10 kg:*
  Administer EFV once daily:

Weight (kg)	EFV dose (mg)*†
10 to <15	200
15 to <20	250
20 to <25	300
25 to <32.5	350
32.5 to <40	400
≥40	600

* The dose in mg can be dispensed in any combination of capsule strengths.

† Some experts recommend a dose of 367 mg/m^2 of body surface area (maximum dose 600 mg) because of concern for underdosing, especially at the upper end of each weight band (see *Pediatric Use* for details).

Adolescent (body weight ≥40 kg)/adult dose:

- 600 mg once daily.

Selected Adverse Events

- Rash
- Central nervous system (CNS) symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- Potentially teratogenic
- Lipohypertrophy, although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors.

Special Instructions

- Administer EFV on an empty stomach, preferably at bedtime. Avoid administration with a high-fat meal because of potential for increased absorption.
- Administer Atripla on an empty stomach.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- EFV should be used with caution in female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor).

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Atripla

- Atripla should not be used in pediatric patients <40 kg where the EFV dose would be excessive.
- *Adult dose:* One tablet once daily

- CYP3A4 and CYP2B6 substrate.
- Dosing of EFV in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
- Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product, it should not be used in patients with creatinine clearance (CrCl) of <50 mL/minute or in patients on dialysis.
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers having higher risk of toxicity. (See text for information about therapeutic drug monitoring [TDM] for management of mild or moderate toxicity.)

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Etravirine (ETR, Intelence, TMC 125) (Last updated November 15, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 25 mg, 100 mg, and 200 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are under way.

Antiretroviral-experienced children and adolescents aged 6-18 years (and weighing at least 16 kg):

Weight in kilograms (kg)	Dose
16 kg to <20 kg	100 mg twice daily
20 kg to <25 kg	125 mg twice daily
25 kg to <30 kg	150 mg twice daily
≥30 kg	200 mg twice daily

Adult dose (antiretroviral-experienced patients):

- 200 mg twice daily following a meal

Selected Adverse Events

- Nausea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

Special Instructions

- Always administer ETR following a meal. Area under the curve (AUC) of ETR is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to ETR.
- ETR tablets are sensitive to moisture; store at room temperature in original container with desiccant.
- Patients unable to swallow ETR tablets may disperse the tablets in liquid, as follows: Place the tablet(s) in 5 ml (1 teaspoon) of water, or at least enough liquid to cover the medication, stir well until the water looks milky; if desired, add more water or alternatively orange juice or milk (patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm [>40°C] drinks, or carbonated beverages should be avoided). Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Dosing of ETR in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- Dosing of ETR in patients with renal impairment: Dose adjustment is not required in

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patients with renal impairment.

Metabolism

- ETR is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein (Pgp). It is a substrate for CYP3A4, 2C9, and 2C19.
- Multiple drug interactions (see below).

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Nevirapine (NVP, Viramune) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 200 mg, extended-release 400 mg

Suspension: 10 mg/mL

Dosing Recommendations

Neonate/infant dose (aged <14 days):

- When used for prevention of mother-to-child transmission of HIV see *Perinatal Guidelines*. Treatment dose not defined for infants aged ≤14 days.

Pediatric dose (aged ≥15 days):
See note below about initiation of therapy.

Aged <8 years:

- 200 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

Aged ≥8 years:

- 120–150 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose is left static to achieve the appropriate mg/m^2 dosage as the child grows, as long as there are no untoward effects.

Note: NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P45-metabolizing enzymes, which results in increased drug clearance. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy, increase to the age-appropriate dose administered twice daily. The total daily dose should not exceed 400 mg.

Adolescent/adult dose:

- 200 mg twice daily

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock.

Special Instructions

- Can be given without regard to food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves (see *Major Toxicities*).
- NVP XR tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see text below).
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have liver function tests performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.

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Note: Initiate therapy with 200 mg given once daily for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.

- 400 mg XR once daily (not approved for use in children)

Note: Initiate therapy with 200-mg immediate-release tablet given once daily for the first 14 days. Increase to 400 mg administered once daily if there is no rash or other untoward effects. In patients already receiving full-dose immediate-release NVP, extended-release tablets can be used without the 200-mg lead-in period. Patients must swallow NVP extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of NVP at the same time.

- *NVP in combination with lopinavir/ritonavir (LPV/r):*

A higher dose of LPV/r may be needed. See LPV/r section.

- Shake suspension well and store at room temperature

Metabolism

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites).
- Dosing of NVP in patients with renal failure receiving hemodialysis: An additional dose of NVP should be given following dialysis.
- Dosing of NVP in patients with hepatic impairment: NVP should not be administered to patients with moderate or severe hepatic impairment.

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Rilpivirine (RPV, Edurant, TMC 278) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablet: 25 mg

Combination Tablet:
- *With emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF):*
  RPV 25 mg + FTC 200 mg + TDF 300 mg (Complera)

Dosing Recommendations

Neonate/infant dose:
- Not approved for use in neonates/infants.

Pediatric dose:
- Not approved for use in children. A clinical trial in treatment-naive adolescents (aged 12–18 years) is under way.

Adolescent (>18 years of age)/adult dose (antiretroviral [ARV]-naive patients only):
- 25 mg once daily

Selected Adverse Events

- Depression, mood changes
- Insomnia
- Headache
- Rash

Special Instructions

- Instruct patients to take rilpivirine with a meal of at least 500 calories (a protein drink alone does not constitute a meal).
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- Do not use rilpivirine with proton pump inhibitors.
- Use rilpivirine with caution when co-administered with a drug with a known risk of torsade de pointes (http://www.qtdrugs.org/).
- Use rilpivirine with caution in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

Metabolism

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.

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Atazanavir (ATV, Reyataz) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg, 150 mg, 200 mg, and 300 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants. ATV should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:

- Data are insufficient to recommend dosing in children aged <6 years.

For children aged ≥6 to <18 years:

Weight (kg)	Once-Daily Dose
15–<20 kg	ATV 150 mg + RTV 100 mg, both once daily with food
20–<32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32–<40 kg	ATV 250 mg* + RTV 100 mg, both once daily with food
≥40 kg	ATV 300 mg + RTV 100 mg, both once daily with food

* Dose in mg requires two different capsule strengths of ATV. Additional patient education should be considered to avoid dosing errors (see text for discussion).

- *For treatment-naive pediatric patients who do not tolerate ritonavir (RTV):* **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.** Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children aged <13 years. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see *Pediatric Use*).
- Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular (AV) block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- Increased serum transaminases
- Hyperlipidemia (primarily with RTV boosting)

Special Instructions

- Administer ATV with food to enhance absorption.
- Additional patient education should be considered to avoid dosing errors when prescribing ATV 250 mg because this dose requires 2 different capsule strengths of ATV.
- Because ATV can prolong the electrocardiogram (ECG) PR interval, use ATV with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, special dosing information is indicated (see Drug Interactions for recommendations on dosing ATV when the drug is co-administered with H2 receptor antagonists). When administered with buffered didanosine (ddI) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddI administration.

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Adolescent (aged ≥18–21 years)/adult dose:
Antiretroviral-naive patients:

- ATV 300 mg + RTV 100 mg or ATV 400 mg once daily with food (if unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels [see *Pediatric Use*]).

Antiretroviral-experienced patients:

- ATV 300 mg + RTV 100 mg, both once daily with food.

ATV in combination with efavirenz (EFV) (adults) in therapy-naive patients only:

- ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily at separate times.
- Although ATV/r should be taken with food, EFV should be taken on an empty stomach, preferably at bedtime. EFV should not be used with ATV (with or without RTV) in treatment-experienced patients because EFV decreases ATV exposure.

ATV in combination with tenofovir (TDF) (adults):

- ATV 300 mg + RTV 100 mg + TDF 300 mg, all once daily with food.
- Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is co-administered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive patients receiving PPIs should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted ATV. Co-administration of ATV with PPIs is not recommended in treatment-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients with marked elevations in transaminases before treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

Metabolism

- ATV is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucoronosyltransferase (UGT1A1).
- Dosing of ATV in patients with hepatic impairment: ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
- Dosing of ATV in patients with renal impairment: No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

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Darunavir (DRV, Prezista) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 75 mg, 150 mg, 400 mg, and 600 mg

Oral suspension: 100 mg/mL

Dosing Recommendations

- DRV should not be used without ritonavir (RTV).

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- *Age <3 years:*

Do not use DRV in children younger than age 3 years because of concerns related to seizures and death in infant rats associated with immaturity of the blood-brain barrier and liver metabolic pathways.

- *3 to <18 years of age and weighing ≥10 kg:*

Weight	Dose (both twice daily[a] with food)
10–<11 kg	DRV 200 mg (2 mL) + RTV 32 mg (0.4 ml[b])
11–<12 kg	DRV 220 mg (2.2 mL) + RTV 32 mg (0.4 ml[b])
12–<13 kg	DRV 240 mg (2.4 mL) + RTV 40 mg (0.5 ml[b])
13–<14 kg	DRV 260 mg (2.6 mL) + RTV 40 mg (0.5 ml[b])
14–<15 kg	DRV 280 mg (2.8 mL) + RTV 48 mg (0.6 ml[b])
15–<30 kg	DRV 375 mg (tablets or 3.75 mL oral suspension) + RTV 50 mg (0.6 ml[b])[c]
30–<40 kg	DRV 450 mg + RTV 60 mg (0.8 ml[b])[c]
≥40 kg	DRV 600 mg + RTV 100 mg

[a] *Do not use once-daily dosing in children aged <12 years or in any patient aged <18 years who is treatment-experienced (prior treatment failure). Once-daily dosing*

Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- DRV must be administered with food, which increases area under the curve (AUC) and maximum plasma concentration (C_{max}) by 30%. Drug exposure is not significantly altered by the calorie and fat content of the meal.
- DRV contains a sulfonamide moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75-mg or 150-mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Careful instruction to caregivers is important. Pill burden may have a negative effect on adherence.
- Store DRV tablets and oral suspension at room temperature (25ºC or 77ºF). Oral suspension should be stored in the original container and shaken well before dosing.
- **Do not use once daily for:** children aged <12 years; for youth ages 12–18 years if treatment experienced (prior treatment failure); or in

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(DRV 800 mg + RTV 100 mg can be used in treatment-naive pediatric patients aged 12–18 years and weighing ≥40 kg but is not FDA-approved for this population (see text). Note that the dose in children weighing 10–15 kg is 20 mg/kg body weight per dose, higher than the weight-adjusted dose in heavier (older) children.

[b] *RTV supplied as 80mg/mL oral solution.*

[c] *To enhance palatability—RTV 100 mg twice daily as the tablet formulation may be safely substituted for the liquid formulation for children ≥20 kg, even though the RTV dose is higher.*

Adolescent (aged ≥18 years)/adult dose (treatment-naive or antiretroviral-experienced with no DRV resistance associated mutations):

- DRV 800 mg + RTV 100 mg, both once daily with food.

Adolescent (aged ≥18 years)/adult dose (treatment experienced with at least one DRV resistance-associated mutation):

- DRV 600 mg + RTV 100 mg, both twice daily with food.

those aged ≥18 years if any of these DRV resistance associated mutations are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate.
- Dosing in patients with hepatic impairment: DRV is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering DRV to such patients. DRV is not recommended in patients with severe hepatic impairment.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min). There are no pharmacokinetic data in patients with severe renal impairment or end-stage renal disease.

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Fosamprenavir (FPV, Lexiva) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 700 mg

Oral suspension: 50 mg/mL

Dosing Recommendations

Pediatric dose (aged >6 months–18 years):

- Unboosted FPV (without ritonavir [RTV]) is FDA-approved for antiretroviral (ARV)-naive children aged 2–5 years, but not recommended by the Panel because of low exposures (see text below).
- Boosted FPV (with RTV) is FDA-approved for ARV-naive infants at least 4 weeks of age and for treatment experienced infants at least 6 months of age; however, the Panel does not recommend use in infants younger than 6 months because of similarly low exposures (see text below). If used in infants as young as 4 weeks, it should only be administered to infants born at 38 weeks gestation or greater.

Aged ≥6 months–18 years:

Twice-Daily Dosage Regimens by Weight for Pediatric Patients at Least 6 Months of Age Using Lexiva Oral Suspension With Ritonavir

Weight	Dose FPV + RTV Both twice daily* with food
<11 kg	FPV 45 mg/kg + RTV 7 mg/kg
11 kg–<15 kg	FPV 30 mg/kg + RTV 3 mg/kg
15 kg–<20 kg	FPV 23 mg/kg + RTV 3 mg/kg
≥20 kg	FPV 18 mg/kg + RTV 3 mg/kg

*Not to exceed the adult dose of FPV 700 mg + RTV 100 mg twice daily.

Note: When administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (FPV has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- FPV tablets with RTV should be taken with food. FPV tablets without RTV can be taken with or without food. Pediatric patients should take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine (ddI) should take FPV at least 1 hour before or after antacid or ddI use.
- FPV contains a sulfonamide moiety. The potential for cross sensitivity between FPV and other drugs in the sulfonamide class is unknown. FPV should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well before use. Refrigeration is not required.

Metabolism

- The prodrug FPV is rapidly and almost completely hydrolyzed to amprenavir (APV) by cellular phosphatases in the gut as it is absorbed.

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twice daily, can be used in patients weighing ≥39 kg. RTV pills can be used in patients weighing ≥33 kg.

Once-daily dosing is not recommended for any pediatric patient.

Adolescent (aged >18 years)/adult dose:

- Dosing regimen depends on whether the patient is ARV naive or ARV experienced.

ARV-naive patients:

- *Boosted with RTV, twice-daily regimen:* FPV 700 mg + RTV 100 mg, both twice daily.
- *Boosted with RTV, once-daily regimen:* FPV 1400 mg + RTV 100–200 mg, both once daily.

Protease inhibitor (PI)-experienced patients:

- FPV 700 mg + RTV 100 mg, both twice daily.

Once-daily administration of FPV + RTV is not recommended.

FPV in combination with efavirenz (EFV) (adults):

- Only FPV boosted with RTV should be used in combination with EFV.
- *Twice-daily regimen:* FPV 700 mg + RTV 100 mg, both twice daily + EFV 600 mg once daily.
- *PI-naive patients only, once-daily regimen:* FPV 1400 mg + RTV 300 mg + EFV 600 mg, all once daily.

FPV in combination with maraviroc (MVC) (adults):

- See MVC section for dosing of FPV with MVC.

- APV is a cytochrome P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.
- Dosing in patients with hepatic impairment: Dosage adjustment is recommended. Please refer to the package insert.

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Indinavir (IDV, Crixivan) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg, 200 mg, and 400 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:

- Not approved for use in children.
- A range of IDV doses (234–500 mg/m^2 of body surface area) boosted by low-dose ritonavir (RTV) have been studied in children (see text).

Adolescent/adult dose:

- 800 mg IDV + 100 or 200 mg RTV every 12 hours

Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- When given in combination with RTV, meal restrictions are not necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If co-administered with didanosine (ddI), give IDV and ddI ≥1 hour apart on an empty stomach.
- IDV capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate
- Dosing in patients with hepatic impairment: Decreased dosage should be used in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg IDV every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

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Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric oral solution: 80 mg/20 mg LPV/r/per mL (contains 42.4% alcohol by volume)

Film-coated tablets: 100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r

Dosing Recommendations

Neonatal dose (<14 days):

- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days.

Dosing for individuals not receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV)

Infant dose (14 days–12 months):

- Once-daily dosing is **not** recommended.
- 300 mg/75 mg LPV/r per m^2 of body surface area twice daily.

  NOTE: Use of 300 mg/75 mg LPV/r per m^2 of body surface area in infants aged 12 months or younger is associated with lower LPV trough levels than those found in adults; in infants, LPV dosing should be adjusted for growth at frequent intervals (see text below).

Pediatric dose (>12 months–18 years):

- Once-daily dosing is **not** recommended.
- 300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily is routinely used by many clinicians, especially for patients previously treated with antiretroviral drugs or when decreased sensitivity to LPV is suspected because of clinical history or documented by resistance testing (see text below).
- 230 mg/57.5 mg LPV/r/m^2 of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients older than age 1 year. For patients already receiving LPV/r, immediate dose reduction at age 12 months is not recommended; many practitioners would allow patients to "grow

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
- Asthenia
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and torsade de pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see *Major Toxicities* below).

Special Instructions

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. Do not crush or split tablets.
- LPV/r oral solution should be administered with food, as a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see *Pediatric Use*).
- LPV/r oral solution can be kept at room temperature up to 77°F (25°C) if used within 2 months. If kept refrigerated (2° to 8°C or 36° to 46°F) LPV/r oral solution remains stable until the expiration date printed on the label.

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into" the 230 mg/m^2 dosage as they gain weight over time (see text below). Some would continue the infant dose (300 mg/m^2 of body surface area per dose twice daily) while on LPV/r liquid formulation.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents

	Recommended number of 100 mg/25 mg LPV/r Tablets Given Twice Daily	
Dosing target	300 mg/m^2/dose given twice daily	230 mg/m^2/dose given twice daily
Body Weight (kg)		
15–20 kg	2	2
>20–25 kg	3	2
>25–30 kg	3	3
>30–35 kg	4[a]	3
>35–45 kg	4	4
>45 kg	4 or 5[b]	4

[a] Note that 4 of the 100 mg/25 mg LPV/r tablets can be substituted by 2 tablets each containing 200 mg/50 mg LPV/r, but the 200 mg/50 mg LPV/r tablets are bigger and may be difficult to swallow

[b] ***In patients receiving concomitant NVP, EFV, FPV, or NFV***, for body weight >45 kg, the FDA-approved adult dose is 500 mg/125 mg LPV/r twice daily, given as a combination of two tablets of 200/50 mg LPV/r and one tablet of 100 mg/25 mg LPV/r. Some Panel members would use 600 mg/150 mg LPV/r for ease of dosing.

Adult dose (>18 years):

- 800 mg/200 mg LPV/r once daily; **or**
- 400 mg/100 mg LPV/r twice daily.
- Do **not** use once-daily dosing in children or adolescents, or in patients receiving concomitant therapy with NVP, EFV, FPV, or NFV, or in patients with three or more LPV-associated mutations (see *Special Instructions* for list):

***In patients with three or more LPV-associated mutations* (see *Special Instructions* for list):**

- The panel generally does not recommend once-daily dosing of LPV/r for children aged <18 years because of high variability of its metabolism in children.
- Do not use once daily if three or more of the following LPV resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- Cytochrome P (CYP) 3A4 inhibitor and substrate.
- Dosing of LPV/r in patients with hepatic impairment: LPV/r is primarily metabolized by the liver. Caution should be used when administering LPV to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, the RTV acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

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- 400 mg/100 mg LPV/r twice daily.

Dosing for individuals receiving concomitant NVP, EFV, FPV, or NFV. *(These drugs induce LPV metabolism and reduce LPV plasma levels; increased LPV/r dosing is required with concomitant administration of these drugs.)*

- Once-daily dosing should **not** be used.

Pediatric dose (>12 months to 18 years):

- 300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

Adult dose (>18 years):

- Food and Drug Administration (FDA)-approved dose is 500 mg/125 mg LPV/r twice daily, given as a combination of two tablets of 200/50 mg LPV/r and one tablet of 100 mg/25 mg LPV/r. Most Panel members would use 600 mg/150 mg LPV/r for ease of dosing. Once-daily dosing should **not** be used.

LPV/r in combination with saquinavir (SQV) hard-gel capsules (Invirase) or in combination with maraviroc (MVC):

- SQV and MVC doses may need modification. See sections on SQV or MVC.

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Nelfinavir (NFV, Viracept) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonate/infant dose:

- NFV should not be used for treatment in children aged <2 years.

Pediatric dose (2–13 years of age):

- 45–55 mg/kg twice daily.

Adolescent/adult dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily.
- Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring to guide appropriate dosing.

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia
- Serum transaminase elevations

Special Instructions

- Administer NFV with meal or light snack.
- If co-administered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- Patients unable to swallow NFV tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, patients should mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.

Metabolism

- CYP2C19 and 3A4 substrate.
- Metabolized to active M8 metabolite.
- CYP3A4 inhibitor.

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Ritonavir (RTV, Norvir) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral solution (contains 43% alcohol by volume): 80 mg/mL

Capsules: 100 mg

Tablets: 100 mg

Dosing Recommendations

RTV as a pharmacokinetic (PK) enhancer:
The major use of RTV is as a PK enhancer of other protease inhibitors used in pediatric patients and in adolescents and adults. The dose of RTV recommended varies and is specific to the drug combination selected. See dosing information for specific protease inhibitors (PIs).

In the unusual situation when RTV is prescribed as sole PI:

- See manufacturer guidelines.

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Paresthesias (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

Special Instructions

- Administer RTV with food to increase absorption and reduce GI side effects.
- If RTV is prescribed with didanosine (ddI), administer the drugs 2 hours apart.
- Refrigerate RTV capsules only if the capsules will not be used within 30 days or cannot be stored below 77°F (25°C). RTV tablets are heat stable.
- Do not refrigerate RTV oral solution; store at room temperature (68–77°F or 20–25°C). Shake the solution well before use.
- RTV oral solution has limited shelf life; use within 6 months.
- Patients who have persistent or significant nausea with the capsule may benefit from switching to the tablet. Also, the tablet is smaller than the capsule and thus easier to swallow.

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To increase tolerability of RTV oral solution in children:

- Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
- Before administration, give a child ice chips, a popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds, or give peanut butter to coat the mouth.
- After administration, give a child strong-tasting foods such as maple syrup, cheese, or highly flavored chewing gum.

Metabolism

- Cytochrome P (CYP)3A4 and CYP 2D6 inhibitor; CYP3A4 and CYP1A2 inducer.

Dosing of RTV in patients with hepatic impairment:

- RTV is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. Data are unavailable on RTV dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.

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Saquinavir (SQV, Invirase) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Hard-gel capsules: 200 mg

Film-coated tablets: 500 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- Not approved for use in children.

Investigational doses in treatment-experienced children:

- SQV must be boosted with ritonavir (RTV):

Aged <2 years:

- No dose has been determined.

Aged ≥2 years (conditional dosing based on limited data, see text):

Weight (kg)	Dose SQV + RTV
5–<15 kg	SQV 50 mg/kg + RTV 3 mg/kg, both twice daily
15–40 kg	SQV 50 mg/kg + RTV 2.5 mg/kg, both twice daily
≥40 kg	SQV 50 mg/kg + RTV 100 mg, both twice daily

Aged ≥7 years in combination with lopinavir/ritonavir (LPV/r) for salvage therapy (conditional dosing based on limited data, see text):

- SQV 750 mg/m^2 (max 1600 mg) or SQV 50 mg/kg have been used in combination with LPV/r, both twice daily.

Adolescent (aged ≥16 years)/adult dose:

SQV should **only** be used in combination with RTV or LPV/r (never unboosted).

- SQV 1000 mg + RTV 100 mg, both twice daily.
- SQV 1000 mg + LPV/r 400/100 mg, both twice daily.

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and ventricular tachycardia (torsades de pointes) have been reported.

Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram (ECG) is recommended and SQV is not recommended in patients with a prolonged QT interval.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor, 90% metabolized in the liver.
- Use in patients with hepatic impairment: Use with caution.

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Tipranavir (TPV, APTIVUS) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral solution: 100 mg TPV/mL with 116 International Units (IU) vitamin E/mL

Capsules: 250 mg

Dosing Recommendations

TPV must be used with ritonavir (RTV) boosting. The RTV boosting dose used for TPV is higher than that used for other protease inhibitors (PIs).

Pediatric dose (aged <2 years):

- Not approved for use in children aged <2 years.

Pediatric dose (2–18 years of age):

Not recommended for treatment-naive patients.

- *Body surface area dosing:*
  TPV 375 mg/m^2 + RTV 150 mg/m^2, both twice daily.
- *Maximum dose:*
  TPV 500 mg + RTV 200 mg, both twice daily.
- *Weight-based dosing:*
  TPV 14 mg/kg + RTV 6 mg/kg, both twice daily.
- *Maximum dose:*
  TPV 500 mg + RTV 200 mg, both twice daily.

Adult dose:

Not recommended for treatment-naive patients.

- TPV 500 mg (two 250-mg capsules) + RTV 200 mg, both twice daily.

Selected Adverse Events

- Rare cases of fatal and non-fatal intracranial hemorrhage
- Skin rash
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia.

Special Instructions

- Administer TPV and RTV together with food.
- TPV oral solution contains 116 IU vitamin E/mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- TPV contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.
- Store TPV oral solution at room temperature 25°C (77°F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.
- Store unopened bottles of oral TPV capsules in a refrigerator at 2° to 8°C (36°–46°F). Once bottle is opened, capsules can be kept at room temperature (maximum of 77°F or 25°C) if used within 60 days.
- Use TPV with caution in patients who may be at risk of increased bleeding from trauma,

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surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding, such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

- Use of TPV is contraindicated in patients with moderate or severe hepatic impairment.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate.
- Dosing in patients with renal impairment: No dose adjustment required.
- Dosing in patients with hepatic impairment: No dose adjustment required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

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Enfuvirtide (ENF, T-20, Fuzeon) (Last updated August 11, 2011; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Lyophilized powder for injection:

- 108 mg vial of ENF. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

Convenience kit:

- 60 single-use vials of ENF (90-mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes

Dosing Recommendations

Pediatric/adolescent dose (aged 6–16 years):

- *Children aged <6 years:*
  Not approved for use in children aged <6 years.
- *Children aged ≥6 years:*
  2 mg/kg (maximum dose, 90 mg [1 mL]) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Adolescent (aged >16 years)/adult dose:

- 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Selected Adverse Events

- Local injection site reactions.
- Increased rate of bacterial pneumonia (unclear association).
- Hypersensitivity reaction (HSR)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of subcutaneous (SQ) injections. ENF injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject ENF immediately or keep refrigerated in the original vial until use. Reconstituted ENF must be used within 24 hours.
- ENF must be given SQ; severity of reactions increases if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions apply ice or heat after injection or gently massage injection site

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to better disperse the dose. There are reports of injection-associated neuralgia and parasthesia if alternative delivery systems, such as needle-free injection devices, are used.

- Advise patient/caregiver of the possibility of an HSR; instruct them to discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with an HSR.

Metabolism

- Catabolism to constituent amino acids.

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Maraviroc (MVC, Selzentry) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 150 mg and 300 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- Not approved for use in children aged <16 years.
- A pediatric clinical trial is under way

Adolescent (aged >16 years)/adult dose:

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including protease inhibitors (PIs) (except tipranavir/ritonavir [TPV/r])	150 mg twice daily
When given with nucleoside reverse transcriptase inhibitors (NRTIs), enfuvirtide (ENF), TPV/r, nevirapine (NVP), raltegravir (RAL), and drugs that are not potent CYP3A inhibitors or inducers	300 mg twice daily
When given with potent CYP3A inducers including efavirenz (EFV) and etravirine (ETR) (without a potent CYP3A inhibitor)	600 mg twice daily

Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Orthostatic hypotension (especially in patients with severe renal insufficiency)

Special Instructions

- Conduct testing with HIV tropism assay (see Antiretroviral Drug-Resistance Testing in the main body of the guidelines) before using MVC to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Use MVC in patients with only CCR5-tropic virus. Do not use if CXCR4 or mixed/dual-tropic HIV is present.
- MVC can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) substrate
- Dosing of MVC in patients with hepatic impairment:

  Use caution when administering MVC to patients with hepatic impairment. Because MVC is metabolized by the liver,

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concentrations in patients with hepatic impairment may be increased.

- Do not use MVC in patients with creatinine clearance (CrCl) <30 mL/min who are receiving potent CYP3A4 inhibitors or inducers.
- Dosing of MVC in patients with renal impairment:

  Refer to the manufacturer's prescribing information

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Raltegravir (RAL, Isentress) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets*: 400 mg (film-coated poloxamer tablet)

Chewable Tablets: 100 mg (scored) and 25 mg
* Film-coated tablets and chewable tablets are not interchangeable.

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

Children aged 2 to <12 years:

- <25 kg: Chewable tablet twice daily to maximum of 300 mg twice daily (see table)
- ≥25 kg: 400 mg film-coated tablet twice daily OR chewable tablets (see table)

Dosing of chewable tablets in children aged 2 to <12 years of age

Body Weight (kg)	Dose	Number of Chewable Tablets
10 to <14	75 mg twice daily	3 X 25 mg twice daily
14 to <20	100 mg twice daily	1 X 100 mg twice daily
20 to <28	150 mg twice daily	1.5 X 100 mg twice daily
28 to <40	200 mg twice daily	2 X 100 mg twice daily
≥40	300 mg twice daily	3 X 100 mg twice daily

Adolescent (≥12 years of age)/adult dose:

- 400 mg film-coated tablet twice daily

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache
- Fever
- Creatine phosphokinase (CPK) elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Can be given without regard to food.
- Chewable tablets may be chewed or swallowed whole.
- Film-coated tablets and chewable tablets are not interchangeable. Chewable tablets have better bioavailability than the film-coated tablets. Chewable tablets should be stored in the original package with desiccant to protect from moisture.

Metabolism

- Uridine diphosphate glucotransferase (UGT1A1)-mediated glucuronidation.
- Dosing of RAL in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- Dosing of RAL in patients with renal impairment: No dosage adjustment necessary.

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Elvitegravir (EVG) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Only available in fixed-dose combination tablets (Stribild):

Elvitegravir (EVG) + cobicistat (COBI) + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF)

EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg

Dosing Recommendations

Pediatric dose (aged <18 years):

- Not FDA-approved or -recommended for use in children aged <18 years.

Adult dose (aged ≥18 years):

- 1 tablet once daily in antiretroviral (ARV) treatment-naive adults.

Selected Adverse Events

- Diarrhea, nausea, flatulence
- Renal insufficiency
- Cobicistat alters tubular secretion of creatinine, and therefore, may decrease creatinine-based estimates of glomerular filtration rate without a true change in glomerular filtration.
- Decreased bone mineral density (BMD)

Special Instructions

- Administer with food.
- Monitor estimated creatinine clearance, urine glucose, and urine protein; in patients at risk of renal impairment, also monitor serum phosphate. Patients with increase in serum creatinine >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before use of FTC or TDF. Severe acute exacerbation of HBV can occur when FTC or TDF are discontinued; therefore, monitor hepatic function for several months after therapy with FTC or TDF is stopped.
- Not recommended for use with other ARV drugs.

Metabolism

- Stribild should not be initiated in patients with estimated creatinine clearance (CrCl) <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

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